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Southwestern MEDICINE

VOL. XXXVII AUGUST, 1956 No. 8

CURRENT THERAPY

The Present Status of Antibiotics

By Chester D. Awe, M. D., El Paso*

When penicillin was first released during World War II, it proved highly effective against almost all gram positive cocci and many of the gram negative cocci and spirochetes. At first, it was carefully rationed and given in small amounts, usually from 100,000 to 300,000 units per patient.

Toward the end of the war reports were circulated which revealed that certain strains of staphylococci were becoming penicillin resistant.

Within the next five years, streptomycin, chloromycetin, aureomycin and terramycin were developed and tried in many types of bacterial infections. According to Jackson and Dowling of the University of Illinois, during 1951, various companies in the United States produced 324 tons of penicillin or approximately two million units for every person in the country.

167 Tons

During the same year, 167 tons of streptomycin were produced, enough to treat one million persons with pulmonary tuberculosis for one year. By 1951, chloromycetin, aureomycin and terramycin had been in production for only two or three years and by that time, 250 tons of these three antibiotics were produced, which was a sufficient amount to provide for about two hundred million patient days of treatment.

More than one half of all prescriptions written in 1951 were for antibiotics. Since 1951, we have had the erythromycin drugs and the newer tetracyclines. During the past five years several facts have emerged concerning antibiotics.

Highly Resistant

One is that in the larger hospitals and to a lesser extent in larger cities of England, Canada and the United States, a high percentage of staphylococci have become resistant to penicillin and, in many instances, to all of the other antibiotics.

Finland and his co-workers isolated 500 strains of staphylococci and found that 75 per cent of them were penicillin resistant. Many of the gram negative bacilli are also becoming resistant to most of the antibiotics. In the past, Professor L. P. Garrod, of the University of London, has published many articles concerning antibiotics.

Joint Meeting

At a joint annual meeting of the British and Canadian Medical Associations held in Toronto, Canada in June, 1955, Professor Garrod discussed the use and abuse of these drugs. He said that the various sulfonamides had similar antibacterial activities, whereas the antibiotics were much more selective in action, except that all the tetracyclines acted similarly.

He pointed out that it is difficult for the clinician to keep up with all the new developments, particularly the new dosage forms. There were, at that time, forty-seven different dosage forms of penicillin.

Persistent Blood Level

With regard to penicillin therapy it is better to have a persistent, even if low, blood level than a high, but short-lived, level. According to Professor Garrod, the indications for the use of antibiotics in different conditions can be divided into the absolute and the conditional.

The use of penicillin is specific in scarlet fever, lobar pneumonia, gonorrhea, and syphilis; streptomycin is effective in tuberculosis and tularemia; chloramphenicol is effective in typhoid fever; and chloramphenicol and the tetracyclines are effective in typhus and other rickettsial infections.

Conditional Group

In the conditional group the particular strain or organism may not be sensitive, as with micrococci (staphylococci) in a hospital environment, or the condition may be due to a variety of organisms. The best course in such cases is to use the most likely antibiotic, pending a bacteriological investigation. The dangers of indiscriminate chemotherapy were stressed.

The main abuses are the administration of agents to undiagnosed patients, to patients with nonsusceptible infections, to patients with trivial complaints such as colds, and to patients for prophylactic use.

Chemoprophylaxis

Dr. Garrod felt that chemoprophylaxis is, however, justifiable in major operations on the chest, abdomen,

* Dr. Awe this month is substituting for Dr. Jack A. Bernard, regular conductor of this section.

and brain, in complicated labor, and for prophylaxis in patients with rheumatic fever, but about 90 per cent of the antibiotics prescribed are not justified. In a census of surgical patients more antibiotics were being given for prophylaxis than for treatment.

Apart from the waste of money if improperly used, the antibiotics have dangerous side-effects in a small number of patients. These side-effects include allergic responses, aplastic anemia, and fulminating, resistant micrococcic enteritis. Chemoprophylaxis is not needed in aseptic operations, normal labor, or ordinary dental work.

Doctor Tempted

It is regrettable that in Britian the hospital doctor is tempted to use chemoprophylaxis as a protection against litigation should any untoward incident occur. At a meeting of the Royal Society of Medicine, Professor Garrod said that penicillin was the antibiotic of choice.

He said that infections could be grouped into those that could be treated immediately with antibiotics (e. g., typhoid with chloramphenicol) and those that needed bacteriological study and control, such as infections with micrococci and gram negative organisms, which are unpredictable. Micrococci are becoming increasingly resistant to all antibiotics.

Erythromycin

As erythromycin is one of the latest antibiotics, Professor Garrod suggested that it should not be used extensively but kept in reserve as the last line of defense to combat organisms resistant to other antibiotics.

One of the most dangerous side-effects of aureomycin and terramycin is the production of a severe and sometimes fatal enteritis due to resistant micrococci.

The best antibiotic against Escherichia coli and Ps. aeruginosa is polymyxin, which may be given intramuscularly and intrathecally if necessary. It may be lifesaving in some forms of meningitis.

Professor Garrod severely criticized the use of two or more antibiotics together.

Synergistic Effect

Sometimes penicillin and streptomycin have to be given together for their synergistic effect, as in endocarditis due to Streptococcus fecalis or peritonitis after perforation of the intestine, but he doubts if there is any other genuine indication apart from these.

Dr. Maxwell Finland from the Harvard Medical School has been particularly interested for the past several years in the antibiotic resistant micrococcic (S. Aureus) infections.

He states that the percentage of penicillin resistant strains isolated from the patients in large hospitals in various parts of the world has increased steadily during the past few years.

Many Strains Resistant

In most of them, three-fourths of all such strains are now highly resistant to this antibiotic. The incidence of penicillin resistant strains of staphylococci isolated from out-patients is much lower (about one-half to one-third) than among in-patients in the hospital.

In some large cities of the United States and Great Britian about ten to thirty per cent of the strains of staphylococci isolated from the nose and throat of normal patients in the community are resistant to penicillin.

A recent study carried out by workers in the Army Medical Service Graduate School showed that micrococci isolated from cutaneous lesions in such places as tropical Mexico or British North Borneo, where there is only minimal use of penicillin, are all sensitive to penicillin in low concentrations and within a very narrow range of such concentrations.

Washington Hospitals

More than one-half of the strains from Washington hospitals were found to be highly resistant to penicillin in the same study. Studies in which the resistance of micrococci to several antibiotics has been tested simultaneously have indicated that almost all strains that are resistant to streptomycin or to the tetracycline antibiotics are also resistant to penicillin.

The situation with respect to erythromycin in some localities has recapitulated within a brief period the longer experience with penicillin.

In one Chicago hospital the intensive use of this agent in preference to others has led to an increase in the incidence of erythromycin-resistant micrococci among hospital personnel from 0 to 75 per cent within a period of five months.

High Incidence

This high incidence dropped to approximately thirty-five per cent a few months after the use of erythromycin was discontinued.

Professor Finland concludes that there is little doubt that the widespread use of antibiotics has given rise to changes in the frequency with which certain common varieties of bacterial infections are encountered, particularly in hospitals. Pneumococcic and hemolytic streptococcic infections are now relatively much less frequent than they were several years ago, and when seen they are now rapidly eradicated.

Infections Encountered

However, infections due to such organisms as Pseudomonas, Proteus and Aerobacter, the majority of which are moderately or highly resistant to most of the commonly used antibiotics, are being encountered with increasing frequency, and in some hospitals infections with Candida (Monilia) are also being encountered.

On the other hand, except as just noted, there is little evidence that most of the common pathogenic organisms other than micrococci have increased in their resistance to penicillin to any important degree.

In particular, there has been no significant increase in resistance to any of the commonly used antibiotics among strains of hemolytic streptococci, pneumococci, Hemophilus influenzae, gonococci and meningococci, and Streptococcus viridans (from cases of subacute bacterial endocarditis).

Gonococci

In the case of gonococci and group A hemolytic streptococci, this has been true even in groups of patients who have recently been under treatment with penicillin or who have been under continuous or intermittent prophylaxis with this agent.

Reports from medical centers in Western Europe and South America reveal results from antibiotic therapy almost identical to those experienced in this country and the United Kingdom.

In other countries, for example in Austria, the situation is somewhat different.

Antibiotics Unnecessary

At a meeting of the Society of Physicians of Vienna in January, 1955, Dr. L. Bohler stated that in the treatment of ordinary wounds antibiotics as a rule are not necessary, for in new wounds thorough debridement and in infected wounds the release of tension by suitable incisions are the essential factors. Since 1954 over 11,000 wounds were debrided and in over 10,000 of these, no antibiotic was used. In El Paso, the problem of superinfection up to the present time has been of minor significance.

Alert To Dangers

Our hospital pathologists are alert to the dangers of wound infections and cross infections. They have made many bacteriologic surveys involving operating room personnel and equipment. In one of our larger hospitals, nose and throat cultures of the operating room personnel revealed that twenty-five per cent of the persons studied had pure cultures of non hemolytic staphylococci which were penicillin resistant.

Conclusion

From the examples cited from different parts of the world, we may conclude that:

(1) In the opinion of many writers, antibiotics are too often used in cases where they are not indicated, such as the common cold, the various virus infections and in most pre-operative cases.

(2) Penicillin, streptomycin and the sulfonamides are synergistic but antagonistic to the tetracycline group. It has been shown that patients with pneumococci meningitis have a much better chance for recovery when penicillin is used alone than when used in combination with other drug such as aureomycin or terramycin.

(3) Bacterial sensitivity tests made in the larger hospitals or in homes where antibiotics have been frequently used are now of little value because of the increasing number of resistant germs, particularly staphylococci. Resistance to the antibiotics is likely to increase and greater precautions must be taken to preserve asepsis in the operating rooms.

(4) If a patient has not responded to a given antibiotic within seventy-two hours, it might be wise to change to some other drug.

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"I am all thumbs today, aren't I?"

APHORISMS and MEMORABILIA

Miscellaneous Truths and Concepts

By Andrew M. Babey, M. D., Las Cruces, N. M.

1. "It is right that we should examine and consider every new thing that is presented to us, but not necessarily right that we should adopt it. Most new things turn out in the end to be wrong." Sir Heneage Ogilvie; The Lancet; Jan. 21, 1956; p. 115

2. "Sciatica is nearly always due to disc protrusion; yet before discs were invented, sciaticas all got well eventually, and now the great majority get well with rest and remain relieved while they wear a belt. Operation is necessary in the uncommon case of definite root pain that cannot be relieved; but while removal of the disc will relieve the root pain, it often makes the backache worse." Ogilvie; loc. cit.; p. 117

3. "The consensus of surgical opinion today is that in cancer of the head or the body a simple short-circuiting operation will, on the average, give a longer survival. In cancer of the ampulla, however, symptoms, signs, and radiological appearances allow early diagnosis, and the results of radical surgery are excellent." Ogilvie; loc. cit.; p. 117

4. "A thing becomes orthodox only when it is considered good by the majority; and when a surgical procedure has been heard of by the majority, tested by the majority, and approved by the majority it is certainly out of date, and probably wrong." Oglivie; loc. cit.; p. 117

Billroth-I

5. "I fear that Billroth-I operation may be condemned as gastrectomy is condemned in some quarters today—not because it is a bad operation, but because it is done badly." Oglivie; loc. cit.; p. 118

6. "Unexplained fever, especially if repeated, after the injection of an organic mercurial is, in our opinion, an indication to stop giving that preparation and to use a different one. Attempts to establish the guilt of the original compound are not without risk to life." Smallwood, W. C., Matthews, H. L.; The Lancet; Jan. 21, 1956, p. 123

7. "Primary hyperaldosteronism was first described by Conn in 1954, and during the past eighteen months about a dozen similar cases have been recognized, although not all have yet been reported in the medical press. The cause of the condition is an adrenocortical tumor—usually an adenoma but ocassionally a carcinoma—which secretes excessive amounts of aldosterone. The clinical picture is characterized by intermittent muscular pains, cramps, weakness, and paralysis; hypertension; renal dysfunction shown by polyuria, nocturia, and albuminuria; and in some casers by pins-and-needles and tetany. The laboratory findings are hypokalaemia, mild hypernatraemia, alkalosis, and inability of the kidney to secrete an acid urine after a loading dose of ammonium chloride." The Lancet; Jan. 21, 1956; p. 212

8. "Most definitions of diabetic neuropathy say that the symptoms include not only pain and paresthesias but usually mention postural hypotension and edema as if they were among the very common features in diabetic neuropathy, which, I think, is not true." Howard Root; American Practitioner; Feb. 1956; p. 292

Neuropathic Conditions

9. "Some neuropathic conditions, which seem to be limited to the extremities, often are accompanied by emotional and cerebral symptoms. At one time we tested our diabetic patients in the hospital with ordinary memory tests. We found that patients when first admitted with uncontrolled diabetes gave poor responses to such simple tests as remembering telephone numbers, and yet ten days or two weeks later did much better." Root; loc. cit.; p. 293

10. "The heart failure in salt-water drowning is almost certainly due to prolonged and severe myocardial anoxia." K. W. Donald; British Medical Journal: July 16, 1955; p. 156

11. "Respiratory failure (in drowning) occurs some time before irreversible circulatory failure in a high proportion of cases." Donald; loc. cit.; p. 156

12. "If a victim has flooded his lungs with fresh water and yet has been sucessfully resuscitated then it would appear certain that he would be suffering from plethora, haemodilution, electrolyte disturbance, and pulmonary oedema. Further, he would be in danger of severe renal damage from the presence of freely circulating haemoglobin." Donald loc. cit.; p. 157

13. "The findings described would suggest that submersion in fresh water is far more lethal than in salt water, yet reliable figures are sadly lacking." Donald; loc. cit.; p. 157

No Time To Waste

14. "It is obvious that not a second, literally not a second, can be wasted. Artificial respiration of some sort must be started as the victim is landed, even at the risk of other injuries. No time should

be wasted in clearing the airways, loosening clothes even at the neck, feeling the pulse, listening for the heart action, draining of the lungs, or selecting of suitable slope so that the head is down. If another person is available then he can clear any material from the mouth and check the tongue position, but such manoeuvers must not interfere with unremitting artificial respiration." Donald; loc. cit.; p. 158

15. "Detailed clinical examination before at least 15 minutes efficient artificial respiration has been carried out may well be a lethal procedure, and it is possible that a person with medical knowledge may even constitute a threat in this respect. If the victim has irreversible circulatory failure then nothing has been lost by delaying the diagnosis. If he has only respiratory failure then prompt and continued artificial respiration may save his life." Donald; loc. cit.; p. 158

16. "There will be the victims with irreversible circulatory failure due either to ventricular fibrillation (fresh water) or to anoxic myocardial failure (salt water); these cannot be saved by artificial respiration." Donald; loc. cit.; p. 158

17. "There will be those who are in respiratory failure without circulatory failure. Those from fresh water have probably less than a minute before the fatal event of ventricular fibrillation, and although such people may ocassionally be snatched from the jaws of death it must be a very rare event. Nevertheless, it emphasized that some chest movement should be initiated almost as the victim is brought out of the water. In salt-water drowning, where only respiratory failure has occurred, there may be a longer period before circulatory death occurs in some cases, but in animal experiments this period can be very short indeed." Donald; loc. cit.; p. 158

Extreme Urgency

18. "The extreme urgency of the situation makes it unwise to think in terms of rocking stretchers, oxygen therapy, or "stimulating" injections. Manual ventilation is as efficient as any portable mechanical apparatus, and even though the apparatus may be brought to the subject it is distracting and the issue is being decided already." Donald; loc. cit.; p. 158

19. "The medical man may arrive after a few minutes' artificial respiration has been carried out, and those present will look to him desperately for expert advice and treatment. He must not stop artificial respiration to examine the chest unless it has continued for at least fifteen minutes. If the heart action is still present then continued artificial respiration is a desperate necessity." Donald; loc. cit.; p. 158

20. "It would be too onerous a responsibility to place a time limit on the resuscitation of drowned persons in general terms, and the decision on how long artificial respiration should be continued must rest with those present on each occasion. As a general rule it should continue for at least an hour. There may not be such miracles, but it is wrong to deny the possibility of one and resist the perhaps hopeless but admirable desire to turn tragedy into triumph. It should, however, be emphasized again and again that it is in the first few seconds after the body has been recovered that prompt action may save life." Donald; loc. cit.; p. 159

Biliary Colic

21. "Clinically, biliary colic usually is felt in the epigastrium and later may localize in the region of the gallbladder. The pain may extend to the right subscapular region, or the midline of the back, or into the chest, or to the left upper abdominal quadrant, or even into either lower abdominal quadrant. Occasionally, the pain may be felt entirely in the left upper abdominal quadrant. It may begin in the back and be projected anteriorly." James F. Weir; Vet. Admin. Tech. Bull.; Sept. 29, 1953; Section 10-92; p. 9

22. "The distended gallbladder seldom is larger than a pear but it may attain the size of a football." Weir; loc. cit.; p. 9

23. "Intrahepatic stones alone are not of common occurrence, but, if multiple small stones are present in the common duct, stones usually are found also in the hepatic ducts." Weir; loc. cit.; p. 9

24. "Jaundice may be absent in a surprising number of cases and this may give a false impression that there is no stone in the common duct . . . . However, given a stone in the common duct, jaundice tends to occur sooner or later. Although it usually follows colic, jaundice may begin painlessly. It may be deep and persistent, usually because of impaction of a stone in the lower end of the common duct. Weir; loc. cit.; p. 11

25. "Paucity or absence of symptoms does not necessarily indicate minimal pathologic change in the gallbladder. Extensive inflammatory changes may be present in the absence of significant symptoms. The number and size of the stones may not be adequately demonstrated by the cholecystrgram. A single stone only may be visualized; yet many small stones, not visualized may also be present. Small stones tend more easily than do large ones to become impacted in the cystic duct or to migrate to the common duct." Weir; loc. cit.; p. 16

Excellent Results

26. "Removal of the gallbladder which contains stones that have been producing colic gives excellent results in 85 - 90 per cent of cases. Mild dyspepsia may persist in some cases . . . Removal of common duct stones gives relief in 75 - 80 per cent of cases. Possibly 10 to 15 per cent of patients continue to have some indigestion and

upper abdominal discomfort. A small percentage (perhaps 5 per cent) have recurring attacks of colic and, in an occasional case, further stones may form in the common duct and further surgical operation may be necessary." Weir; loc. cit.; p. 17

27. "Estimations of the concentration of barbiturate in the urine are of no clinical value, because large doses of barbiturate depress urine secretion. The short-acting and medium-acting barbiturates, being largely destroyed in the body, appear unchanged in only low concentration in the urine, and the presence in urine of other chromogens interferes with the accuracy of the estimation." The Lancet; Feb. 18, 1956; p. 293

28. "It cannot be stressed too strongly that a full epileptiform convulsion is common in quite normal individuals if a syncopal attack is severe and prolonged. A history of injury and loss of sphincter control is therefore less useful than the textbooks would have one believe. The crucial measurement during the attack is the arterial pressure; this is increased in epilepsy and is, of course, greatly decreased in syncope." Sharpey-Schafer; Brit. Med. Journ.; March 3, 1956; p. 509

Aldosterone

29. "Aldosterone proves to be from 50 to 120 times as potent as D. C. A. in controlling the excretion of sodium and potassium by the kidney. Its discovery explains the established clinical fact that, whereas in Addison's disease severe dehydration soon results from excessive loss of sodium in the urine, this does not occur in hypopituitarism when adrenal activity is also very low. In Addison's disease the morbid process destroys the cortical cells which produce aldosterone, thus causing the sodium loss and the potassium retention, but in hypopituitarism production of aldosterone is not affected because it is not dependent on corticotrophin (A. C. T. H.) as is the production of hydrocortisone." Brit. Med. Jour. March 17, 1956; p. 618

30. ". . . . severe potassium depletion, for this alone is now known to damage the kidneys." loc. cit.; p. 618

31. "Thus the interesting situation has become clear that two strikingly different types of clinical picture are both associated with excessive production of aldosterone. The one due to tumour, and clearly primary, is associated with severe loss of potassium; the other, probably secondary, is found in a variety of conditions with excessive retention of sodium and is not associated with appreciable potassium disturbance." loc. cit.; p. 619

32. "Professor McMichael said that the chance of the malignant form developing in a patient with hypertension was about 1 in 200." The Lancet; April 21, 1956; p. 504

Abstract

Feinblatt, T. M. & Ferguson, E. A. Jr., Timed-disintegration capsules, an in vivo roentgenographic study, *New England J. Med.* 254;940 (May 17) 1956.

An in vivo roentgenographic study of timed-disintegration capsules showed that, contrary to the common impression, the contents are scattered widely throughout the length of the gastro-intestinal tract before the individual particles disperse or dissolve. The popular belief that the mass of the capsule contents remains in a single blob, based on an artist's conception, is shown to be erroneous.

In the present study four different kinds of Nyscaps, (Nycso Timed-disintegration capsules), containing radiopaque barium sulfate 5 mg. (substituted for the usual active medication) were used. The first type was for immediate disintegration, the second for timed disintegration in about two hours, the third in about four hours, and the fourth in about six hours. Roentgenograms were taken immediately after ingestion and repeated in two, four, six, eight, and ten hours.

The roentgenographic technique demonstrated a longer disintegration time than the modified U. S. P. method. The disintegration time was two to four hours as compared with two hours by U. S. P. technic, four to six hours as compared with four hours, and six to ten hours as compared with six hours. It is believed that the roentgenographic technic offers a more accurate picture because it is an in vivo method. The great convenience of the timed-disintegration capsule makes it an ideal method for the administration of drugs usually given in three divided doses.

CLINICAL NOTES FROM GRAND ROUNDS

These notes are abstracts of opinions expressed by staff members during case presentations at the Friday Grand Rounds of the Pratt Diagnostic Clinic—New England Center Hospital.

Malignant exophthalmos may develop before there are other signs of hyperthyroidism; it may parallel the clinical course of hyperthyroidism; or it may appear for the first time after hyperthyroidism has been brought under control. It never occurs without some association with hyperthyroidism. It has been theorized in the past that malignant exophthalmos was caused by an excess of thyrotropin, but there is no proof to support this concept. Therapy with thyroid extract which suppresses thyrotropin is probably of no value. Most cases progress rapidly up to a point when spontaneous recovery begins. Small doses of x-ray treatment to the orbits or pituitary fossa may hasten recovery in some cases. It is important to protect the corneas by use of goggles and protective ointments. Because small amounts of excess fat or fluid in the orbits may be critical, a low calorie, low sodium diet should be prescribed.

MONTHLY CLINICAL PATHOLOGICAL CONFERENCE
EL PASO GENERAL HOSPITAL

June 21, 1956

FREDERICK P. BORNSTEIN, M. D., EDITOR — CASE NO. 607
PRESENTATION OF CASE BY DR. JOE C. CARTER

HISTORY

Dr. M. Nathan Kleban:

A 47 year old Latin-American housewife entered this hospital on December 13, 1955, because of an illness of two weeks duration.

The patient experienced epigastric distress, right lower abdominal quadrant and rectal pain associated with defecation, an increase in number of daily bowel movements with stools which were small, hard, and black with bright red blood on the surface.

Anorexia, belching, abdominal swelling and yellow discoloration of the eyeballs occurred.

There were no chills, feverishness or nausea. There was no history of previous jaundice, exposure to liver toxins, injections within the recent past, or previous intolerance to fatty foods. Alcohol consumption had been generous for an unknown period of time.

Past and family history were not relevant to the present illness.

Physical Examination

The patient was an obese, jaundiced woman who appeared moderately acutely and chronically ill. T. 100, P. 90, R. 20, B. P. 116/70.

There were no spider angiomata. The skin was of a "peculiar color". Percussion note was dull and breath sounds were decreased over the left posterior lung field. Four fingers-breadth below the right costal margin a smooth, tender liver edge was felt. Palpation of the abdomen elicited diffuse tenderness. A fluid wave, shifting dullness or splenomegaly were not detected. Hemorrhoids were present. The balance of the physical examination, including pelvic and sigmoidoscopic examinations, contributed no additional significant information.

Hospital Course

Temperature elevations to 100 or 101 occurred almost daily. Rectal pain and abdominal discomfort persisted. Bright blood was present on toilet paper and in water following bowel movements. One stool was described as yellow, none as black. 600 cc. of greenish-yellow fluid were removed from the right pleural space.

An attempt at paracentesis yielded only five cc. of yellow fluid. Venous pressure was 11 cm., decholin arm-to-tongue circulation time was 15 seconds. A low salt diet was taken fairly well. Diamoz, Methiscol, and a multi-vitamin preparation were prescribed.

Penicillin and Streptomycin were administered when the patient complained of pain in her mouth and a swollen jaw. On December 31 the patient was discharged home to return after the first of the year for additional diagnostic studies.

Returns to Hospital

On January 28, 1956, the patient returned to the hospital more heavily jaundiced, with greater abdominal distension, evidence of ascites, presacral and lower extremity pitting edema, basilar pulmonary rhonchi, and a grade two systolic murmur heard at all valve areas but more intense over the mitral area.

Eleven hundred and eighty cc. of straw colored fluid were removed from the peritoneal cavity by paracentesis on one occasion, and 1300 cc. on another. Seventeen hundred cc. of straw colored fluid were aspirated from the right pleural space. The patient vomited, and was restless. She developed a fever beginning on the fifth day, became lethargic, incoherent, stuporous, bled from the mouth and nose, went into shock, then coma, and died two weeks after re-admission.

Laboratory Studies

December 13-31: Urinalysis normal except for presence of bile and absence of urobilinogen. Hemoglobin 9.0 gms. Packed cell volume 32 per cent. WBC 29,400. Stabs 13, seg. 70, Lymphs 12, monos 3, eos 2. Prothrombin time 16 seconds, 65 per cent of control. Van den Bergh 5.2 total, 4.1 direct. Cephalin cholesterol flocculation 4+ in 24 hours. Fasting blood sugar 92 mg per cent. Total cholesterol 213 mg per cent, esters 75 mg. per cent. Alkaline phosphatase 8.0 Bodansky units. Serum albumin 2.6, serum globulin 2.0. Blood urea nitrogen 11.0 mg. per cent. Stool negative for occult blood and urobilinogen. Sputum negative for fungi and acid-fast organisms. Kahn doubtful, Kolmer positive. Pleural fluid: no growth in routine culture, no AFB on culture smear. Peritoneal fluid: no growth on routine culture, 60 per cent pelys, 40 per cent lymphs.

Survey film of abdomen: Findings consistent with ascites and enlarged liver. Chest film: Right pleural effusion and displacement of mediastinum to left. Upper G. I. Series: Esophageal hiatal hernia.

January 28 - February 11: Urinalysis 1.007, acid, albumin 3+, sugar negative, WBC 20-30, RBC 15-20, bile positive, urobilinogen negative (on 8th day). Hemoglobin 9.0 gms., 7.0 gms. Packed cell volume 30 per cent, 22 per cent. WBC 14,700; 27,500. Stabs 7, Segs. 80, Lymphs 13. Moderate hypochromia of red cells. Kahn negative, Kolmer anticomplimentary. Van den Bergh 8.5 total, 6.0 direct; cephalin choles-

terol flocculation 2+ in 24 hours, 3+ in 48 hours. Alkaline phosphatase 8.6 Bodansky units. Prothrombin time 23 seconds, 25 per cent of control. Coombs test negative. Peritoneal fluid: specific gravity 1.003, protein 0, WBC 3, RBC 6, no growth on routine culture. Carbon dioxide combining power: 24 meq/L; chloride 95, 84 meq/L; Sodium 130 meq/L; Potassium 2.1 meq/L. No tumor cells seen on peritoneal fluid smear.

Chest film: Increasing right pleural effusion, shift of mediastinum to left, congestive failure. Abdominal films: ascites.

Electrocardiogram: Somatic tremor, low voltage, Q-T interval greatly prolonged, suggesting electrolyte disturbance.

Clinical Discussion — Dr. Joe C. Carter:

This protocol presents in a very orderly manner just about all possible positive and negative evidence for an etiological-pathological diagnosis of irreversible primary or secondary liver disease with hepatic jaundice and hepatic decompensation. But there are always pitfalls in liver disease diagnosis, even in retrospect.

Primary hemolytic jaundice is immediately ruled out by the relatively unchanging moderate anemia, the increased direct reacting bilirubin, the presence of bile pigments in the urine, and no increased urobilinogen in the urine. Rather marked elevation of the urobilinogen in urine is valuable in directing attention to hemolytic jaundice or acute liver cell necrosis; but all other values are so variable and difficult to interpret, that they are best ignored.

Adequate Kidney Function

There was no evidence for any primary cardiovascular or renal disease. There was adequate kidney function throughout the hospital stay. The attending physicians ruled out constrictive pericarditis.

There was nothing to point to any systemic disease, such as Lupus or polyarteritis. However, Mowry and Lundberg reported that 6 per cent of 230 cases of polyarteritis were diagnosed as primary liver disease.

All of the positive findings point to a severe diffuse disease of the liver parenchyma. The most specific evidence is: *(1)* an enlarged, smooth and tender liver; (2) increased levels of bilirubin in blood and urine; *(3)* low serum albumin and low total protein (in absence of renal disease); *(4)* low prothrombin activity that failed to respond to parenteral vitamin K. Other less specific but very important evidence is the strongly positive cephalin cholesterol flocculation test, and later the positive thymol turbidity test. Of lesser importance is the low percentage of esters and the normal level of cholesterol.

Negative Evidence

The normal total cholesterol value with the normal alkaline phosphatase values are very important negative evidence against primary biliary obstruction (either intra- or extra-hepatic), with or without biliary cirrhosis, although there is the occasional case that progresses to an ultimate pathological state that is almost indistinguishable, clinically and pathologically, from diffuse nodular cirrhosis.

The history and findings in this case are not suggestive of primary biliary tract disease. Cholesterol values in primary biliary tract obstruction tend to be elevated, and at times reach very high levels.

Alkaline phosphatase values (in the absence of bone disease) are often very informative. The normal values of the commonly used tests are:

King-Armstrong	**0-13 units**
Shinowara	**2-9 units**
Bodansky	**1.5 - 5.4 units**

I would like to give some generalized interpretations by Mellinkoff et al in a report from Johns Hopkins: *(1)* The majority of cases of obstructive jaundice will have above 15 Bodansky units, with a normal cephalin flocculation and thymol turbidity test; *(2)* 75 - 95 per cent of the cases of common duct obstruction will have values above 25 Bodansky units; *(3)* most patients with parenchymal liver disease will have elevated cephalin flocculation and thymol turbidity values, with an alkaline phosphatase value near normal or at least below 15 Bodansky units; *(4)* it appears that 15 Bodansky units is the best approximate dividing line between non-obstructive jaundice and uncomplicated obstructive jaundice.

Symptoms Present

With this severe diffuse hepatic cell disease there were ascites, right hydrothorax, and edema. About 75 per cent of the cases of ascites have their origin in portal cirrhosis.

It is said that ascites in cirrhosis is due to intrahepatic venous hypertension rather than to splanchnic venous hypertension, and that the most important factors predisposing to ascitic fluid formation in patients with cirrhosis are lowered osmotic pressure due to depleted serum proteins, particularly albumin, abnormalities in metabolism of salt and water, and more than likely a disturbed hormonal balance.

Thus we do not of necessity have to have portal hypertension in this case—but I suspect that it is present even though no esophageal varices have been demonstrated.

Congestive splenomegaly could also be present. The right hydrothorax needs explaining. It is said that left hydrothorax never originates from portal cirrhosis.

The hydrothorax could be explained by hypertension in the azygos veins from portal hypertension, or on the basis of ascitic fluid going through the diaphragm as in Meig's Syndrome.

Typical Findings

At times primary and metastatic neoplastic diseases of the liver can produce just about all of the typical findings of portal cirrhosis. However, to be really

typical, there should be a diffuse spreading of very small (almost microscopic) nodules.

Hepatomas occur in about six per cent of all cirrhotic livers. They may be grossly nodular and easily distinguished from cirrhosis. Others can produce a picture that is impossible to distinguish from portal cirrhosis, except by liver biopsy.

A rare cholangioma can do the same thing, but is more likely to produce a picture of biliary cirrhosis for sometime. Metastatic lesions from the biliary tract, the pancreas, the gastro-intestinal tract, and other sites will often be confusing, but they usually present a good bit of evidence of obstructive type of jaundice or cirrhosis.

In this case a search was made for all possible sources of any primary neoplasm.

They were apparently quite concerned about an alveolar cell carcinoma in the right lung, and justly so, for a small carcinoma at the periphery of the lung certainly can spread to the liver and produce a portal cirrhosis syndrome. However, I think they have adequately ruled out any malignancy. No tumor cells were found in the transudates.

Down Hill Course

The history of this case suggests alcoholic or nutritional hepatitis rather than viral or toxic hepatitis. The down hill course in the face of adequate supportive treatment; the low proteins and unresponsive prothrombin activity suggest severe hepatic decompensation.

Astute therapy kept the electrolytes well in balance up to a few days before death, when a low potassium was suspected and an electrocardiogram ordered. A few days later a K level was found to be low.

The electrocardiogram was interpreted by Dr. Appel without benefit of clinical information, and we will ask him to review the EKG in the discussion of the case.

Dr. Saul B. Appel:

We see a lot of electrocardiograms like this on the service here and it is really very difficult to say much about them unless you have some specific information, which is one of the reasons why we ask the internes to be specific if they can, because so many things can alter the T-waves in the EKG.

In this case there was low voltage which was compatible with the generalized edema and right hydrothorax. However, the voltage over the left precordium was as expected because the heart was not separated from the electrodes by a large body of short-circuiting fluid, but the pattern in this case of the S-T segments and T-waves would fit in to one of the many patterns that can be seen in hypokalemia.

Severe Disturbance

However, wherever there is a severe disturbance in electrolyte balance, other abnormal electrolyte concentrations are liable to be found and they can affect the T-waves too, so it is very dangerous, I think, to stick your neck out and say, "This is hypopotassemia, this is hyponatremia", etc., and one isolated EKG is always a difficult thing to deal with.

If we have several of them, at least you can say whether or not a trend is going to one direction or another.

So I would encourage those who intend to use the cardiogram to assist in electrolyte control to take several of them and to put the hour of the day down as well as the date, so that there won't be any question later on as to which came first.

Dr. Charles E. Webb:

There is one statement in the protocol about the absence of urobilinogen in the urine on both occasions. Certainly in 90 per cent of the cases this means a malignant extra-hepatic obstruction, and I think it might be a factor here.

Dr. Jack C. Postlewaite:

I see a lesion in the chest X-ray, it seems to be changing and isn't a constant lesion, and perhaps there are flecks of calcium in it. With a changing lesion it could be there is some atelectasis occurring by virtue of the fluid, and everything shifted over here; but the point was made that the urobilinogen was noted to be absent, and one would wonder if there is any correlation between the lung lesion and the abdomen.

Dr. Manley B. Cohen:

The lesion that is pointed out by Dr. Postlewaite is certainly there in the first interspace of the left lung field. I think there are certain technical differences which probably account for the slight change that may appear.

Apparently the first film that we see up here is the last of the X-rays of the chest that were taken and apparently after the fluid was greatly relieved. The original pictures show a large pleural effusion with possibly some atelectasis but I rather think that the shadow seen in the right upper lobe area actually is in the fissure and represents a slight amount of fluid rather than an atelectatic portion of lung.

In the last film which shows a pleural cavity relatively free of fluid there is some haziness in the right lower lobe area but probably this is a simple residual fluid opacity overlying the lung tissue. It may, of course, represent a terminal pneumonia.

Clinical Diagnosis: Cirrhosis of the liver

Dr. Carter's Diagnosis: Cirrhosis of the liver associated with hepatic necrosis.

Pathological Diagnosis: Fatty cirrhosis of the liver associated with sub-acute hepatitis.

Pathological Discussion:

Dr. Frederick P. Bornstein:

On autopsy we found a well nourished 48 year old woman who was markedly jaundiced. The abdomen was distended and a fluid wave could be elicited. Upon opening the body cavities, 2000 cc. of fluid were removed from the peritoneum, 1500

cc. from the right pleural cavity and 400 cc. from the left pleural cavity.

Several caseous, partially calcified areas were present in the lung, obviously tuberculosis, which explains the roentgenological changes referred to by Dr. Postlewaite in the discussion.

Main Interest

The main interest in this case naturally centers around the liver. The liver weighed 1450 grams and was of soft consistency. The surface of the liver was smooth and yellow. The cut surface of the liver showed a complete loss of the normal architectural pattern; instead, one saw very smooth, pale yellow liver parenchyma of rather homogenous type.

The bile ducts were unobstructed and free of stones. My impression upon gross examination was that we were dealing with a sub-acute hepatitis.

Microscopic examination, however, revealed a far-reaching change of the architectural pattern which was caused by the proliferation of dense fibro-connective tissue, sub-division of the liver lobules, and formation of pseudo-lobules, this representing a picture of cirrhosis.

In addition, however, there were profound changes of the liver parenchyma. The individual liver cells show extreme toxic damage, lipoid infiltration and foci of necrosis.

Two Factors

To classify this picture properly we have to take two factors into consideration—the general cirrhotic pattern, and the severe change in the liver parenchyma.

It is my impression that this patient had a slowly proceeding cirrhotic process of the liver upon which a toxic hepatitis was superimposed, producing the rapid death of the patient. The gross appearance of the liver and the clinical course certainly suggest an active hepatitis.

The microscopic changes, however, show an undeniable extensive cirrhotic change in addition to the damage to the liver cells.

Dr. Carter:

Recently I had a case of typical Laennec's cirrhosis, autopsied at Hotel Dieu, with onset of edema and ascites. The patient lived about six weeks. There was much less inflammatory reaction in this case at autopsy. The proteins were very low, it was merely a liver decompensation.

Perhaps there were other things concerned, because we had a very high white count, and we had a high white count in this case and that is why I ignored that. I would like to say something about the question Dr. Webb brought up.

I think perhaps his remarks could be a little misleading because I don't believe the value of urobilinogin in the urine is of any significance unless you get a daily test for 5 or 6 days. I don't know how you can make a diagnosis to differentiate the ultimate change between Laennec's cirrhosis and a post-necrotic cirrhosis.

Dr. Bornstein:

As to the question of post-necrotic cirrhosis; it is not too common a thing. The nodules there are actually a regeneration of liver tissue; the nodules are composed of young, vigorous, regenerating liver cells. In this particular case, this liver is particularly unusual in the lack of any regenerative activity. All you have here is toxic damage and no regeneration whatsoever.

MEETINGS

Southwest Ob-Gyn Meet Scheduled in Tucson

Speakers for the annual meeting of the Southwest Obstetrical and Gynecological Society meeting, to be held in Tucson November 12 and 13, 1956, have been announced by Dr. Hollis H. Brainard, Tucson, president of the Society.

Bayard Carter, M.D., Professor of Obstetrics and Gynecology, Duke University.

Franklin L. Payne, M.D., Professor of Obstetrics and Gynecology, University of Pennsylvania.

Ralph A. Reis, M.D., Professor of Obstetrics and Gynecology, Northwestern University.

E. Stewart Taylor, M.D., Professor of Obstetrics and Gynecology, University of Colorado.

CLINICAL NOTES FROM GRAND ROUNDS

These notes are abstracts of opinions expressed by staff members during case presentation at the Friday Grand Rounds of the Pratt Diagnostic Clinic—New England Center Hospital.

In some cases of subacute bacterial endocarditis the diagnosis may be very difficult because repeated blood cultures are negative. In these, arterial cultures may be taken or the amount of blood usually cultured may be doubled. Even so, cultures may remain negative, possibly because the endocarditis occurs on the tricuspid or pulmonic valves. When continued fever, embolic phenomena, a cardiac murmur and splenomegaly exist without other explanation, antibiotic treatment will have to be instituted without a positive diagnosis. In suspected cases, treatment should be instituted with 1 million units of aqueous penicillin every six hours plus 1 gm. of equal parts of streptomycin and dihydrostreptomycin once daily. The minimum period of treatment is four weeks. Improvement should be noticed within a week and is marked by return of fever to normal, increasing appetite and weight gain.

ORIGINAL ARTICLES

The Management of Viral Hepatitis*

By William I. Coldwell, M. D., El Paso

Since World War II, there has been a marked change in the knowledge and management of viral hepatitis. Although the disease has been recognized in the medical literature for many years, much progress has been made from the previous concept of a benign catarrhal jaundice due to a mucous plug in the common duct, to the present knowledge of the serious sequelae of chronic hepatitis and cirrhosis which may result.

The large number of soldiers with the disease in epidemic form and with complications, made it necessary to devise more sensitive and simpler tests to detect low grade liver impairment. Such liver disease can be diagnosed only by the use of the more sensitive function tests indicating liver cell damage. The new concept of hepatitis without jaundice, was recognized, requiring the use of these tests in diagnosis.

Two Types

The syndrome, viral hepatitis, includes both infectious hepatitis and homologous serum hepatitis. Both are produced by hepatotropic, filtrable viruses causing parenchymal liver damage. In many cases, the diseases cannot be distinguished.

Infectious hepatitis is characterized by an abrupt onset with a preceding prodromal period of fever above 100 degrees F., chills, malaise and anorexia, a latent period of about a week, followed by the development of icterus and other signs of liver disease. The incubation period averages three to six weeks.

Homologous serum hepatitis is characterized by an insidious onset with fever below 100 degrees F. and with absence of other symptoms of infection. The incubation period is usually between two to five months.

Infectious Hepatitis

Infectious hepatitis is spread by oral ingestion of fecally contaminated material. Homologous serum hepatitis is transmitted entirely by parenteral introduction of the virus. This may include blood, plasma, serums, plasma fractions, local use of blood or human thrombin topically, and inadequately sterilized needles, syringes, lancets, etc. used in any skin puncture. Among the earliest recognized epidemics was that following contaminated yellow fever vaccine in World War II.

Specific bacteriological and serological diagnosis of hepatitis cannot be made. A sound evaluation of the history, course and physical findings is of utmost importance in the differential diagnosis of jaundice, and in many cases a definitive diagnosis can be made clinically.

*Presented at Texas District One Medical Association Meeting, Pecos

However, the determination of the cause of jaundice is rarely a medical emergency and injudicious surgery performed on a patient with non-obstructive jaundice is never helpful and usually deleterious. In those patients in whom there is reasonable doubt clinically, the liver function tests are essential.

Important Points

The important clinical diagnostic points in hepatitis are infectious onset, lack of pain, or at the most a dull ache in the right upper quadrant, adenopathy, and an enlarged, smooth, tender liver early in the course of the disease. Jaundice in a younger person that appears rapidly, levels off, and clears in a month is characteristic of hepatitis.

In devising a group of liver function tests, the multiplicity of functions of the liver must be considered. No one test can be completely accurate. One test may give normal results while others may reveal marked impairment. Also, the functioning ability of the liver is constantly changing so that repeated tests are necessary to obtain an index of improvement or failure in the liver.

Memory Refreshed

To refresh your memory concerning the physiology of the liver and bile metabolism, bilirubin is a derivative of hemoglobin liberated from broken down red blood cells. This liberation takes place in the reticulo-endothelial system in various parts of the body including the bone marrow, spleen, lymph glands and connective tissue, including the liver. These tissues are responsible for the extra-hepatic formation of bile pigment, or bilirubin.

Urobilinogen is formed in the bowel as a result of the action of intestinal bacteria on bilirubin. A portion of it is absorbed into the portal system and the normal liver removes it. In the presence of liver disease, large amounts of it are allowed to escape into the urine. In hepatitis, the liver cells are damaged and unable to remove bilirubin from the blood and excrete it into the bile ducts. This leads to an accumulation of bilirubin in the serum and the clinical condition known as jaundice when the excess bilirubin diffuses into the tissues.

Early Tests

The most important early tests in hepatitis are:

1. Serum bilirubin or icteric index. The former is much more accurate and gives evidence of liver disease prior to appearance of frank jaundice. Normal total serum bilirubin is 1.0 mgm. or less.

2. Bromsulfalein excretion. In the absence of jaundice, this test is of value in diagnosis of early liver disease. The dye is given I. V. in the dose of 5 mg./kg. body weight and a single 45 minute blood specimen is drawn. Over 5 per cent retention of the dye is abnormal.

Other Tests

Tests which become abnormal later include:

1. Thymol turbidity. This and the following tests depend on changes in the serum globulin fraction, and indicate liver cell damage. Normal reading is none to five units.

2. Thymol flocculation. Any reading above two plus in 48 hours is abnormal.

3. Cephalin flocculation. Any reading above two plus in 48 hours is abnormal. Many other tests of this type have been devised, but these are the ones I have found most practical. Other tests very helpful if there is difficulty in the diagnosis include:

Further Tests

1. Urinary urobilinogen. Any increase in this test is in favor of hepatitis since it cannot be formed in the presence of complete obstruction of bile. Normal reading is up to one to twenty dilution or one to two Erlich units in a two hour specimen.

2. Alkaline phosphatase. If above 15 Bodansky units, it favors obstruction. The range between five to 15 units may be found in hepatitis.

In an occasional case of early hepatitis, there may be patients whose tests give evidence of obstruction as well as liver cell damage. These are thought to be due to intra-hepatic biliary obstruction and the tests indicating obstruction become negative if followed serially, while those indicating liver cell damage, persist positive. Also, acholic stools often are present early in hepatitis but should change to normal within a few days. This is due to the same mechanism as noted before.

Management

The management of hepatitis, once the diagnosis is established, is as follows:

Rest. Bed rest is indicated because blood flow through the liver is altered in patients with liver disease. Distention of the liver occurs and water balance, as revealed by both decreased urine output and by water tolerance tests is impaired. Rest should be continued until all liver enlargement has subsided, and ideally, until all liver function tests are normal.

However, the thymol turbidity test may be persistently elevated and some activity can be allowed while it is still positive but improving. Graduated exercises are indicated with a longer period of convalesence if the occupation requires long standing or any physical effort. Generally a period of several weeks of complete bed rest plus several more weeks of increasing activity is indicated.

Tests

Tests, especially the bromsulfalein retention should be made at intervals to guide progress. Some authorities allow ad lib activity when the patients feel like it. I usually allow bathroom privileges at the start unless critically ill.

Diet. Early in the disease, complete anorexia is the rule and five to ten per cent glucose, 2000 cc. daily with the addition of a potent B complex and Vitamin C is necessary. Tube feedings are occasionally needed but not well tolerated by most patients. Usually, within one week, intravenous fluids can be discontinued as the appetite returns, and soft frequent oral feedings of cooked cereals, milk, soft boiled eggs, tea, toast, jelly, jello, applesauce and soups are begun. As soon as possible, a full diet of Carbohydrate-350 grams and Protein 150 grams should be used. Fats are given ad lib to allow the diet to be palatable. Formerly, low fat diets were used but patients will usually individually regulate the amount of fats ingested due to some tendency to intolerance to them. Additional sweetened juices and hard candy are added to the diet.

Pure Vitamins

Moderate amounts of pure vitamins orally insure an adequate supply. These should not exceed Thiamin 500 mgm., Nicotinamide 1000 mgm. and Riboflavin 300 mgm. daily. Crude liver extract two cc. daily intramuscularly provides a good source of Vitamin B complex avoiding the possible toxic effects of large doses of pure vitamins, particularly Nicotinic acid parenterally. Brewer's yeast tablets provide an economical source of oral Vitamin B.

Constipation is usual and should be managed with milder laxatives as milk of magnesia. Antacids and antispasmodics may be used for symptomatic relief.

Avoidance of alcohol and drugs that are detoxified by the liver such as morphine, sulfonamides and short acting barbiturates, is important.

Lipotropic Substances

The use of lipotropic substances, such as choline, methionine, betaine, and inositol is debatable. It is doubtful if they are necessary in early hepatitis and may overload the stomach to the exclusion of the more important nutritional elements.

Vitamin B-12 in 1000 mcgm. doses has been reported by some to be of value and shorten the course, but routine use is not indicated.

Antibiotics, especially aureomycin, have been used in the more severe cases with apparent good results, but should not be used in mild cases because of adverse affects on the appetite and frequent disturbing effect on the intestinal flora. They are indicated for secondary infections such as the respiratory and urinary tracts. In severe cases, the dose is 40 mg./kg. body weight intravenously in divided doses daily.

Other Treatments

Other treatment used has included large doses of ascorbic acid and ACTH and cortisone. Gamma glo-

bulin is of no value in treatment, only in prevention which will be discussed later.

A small percentage of cases will present the picture of severe acute, hepatic insufficiency. These were formerly known as acute yellow atrophy and are now known to be a severe fulminating form of viral hepatitis. Here, the prognosis is quite grave. The patient shows irritability and mental confusion, leading to stupor and true coma. Jaundice progressively deepens, fluid retention occurs, with oliguria and a decrease in liver size. Skin and mucous membrane hemorrhages are a terminal sign.

Unsatisfactory

As is to be expected, treatment is unsatisfactory. I usually restrict protein intake to at least 1 gm./kg./day. Sodium restriction is also important. Oxygen, blood transfusions, and general supportive therapy is indicated.

Often hypokalemia occurs and addition of parenteral potassium is necessary. An experimental form of treatment recently advocated is the use of glutamic acid. The mechanism is that it binds ammonia to form glutamine which is metabolized without liberating ammonia. ACTH and cortisone are used in these cases with some good results. As in other illnesses they cause a decrease in fever, jaundice and anorexia but may mask progressive liver failure.

Follow-up

The follow-up of viral hepatitis is both clinical and laboratory. After resumption of activity, twice a month examinations for a period of three months should include weight, general appearance, liver size and palpation for splenomegaly. Laboratory studies include serum bilirubin, at least until normal, bromsulfalein and any other tests that may have been persistently positive. Rechecks should be made at three months and six months following the return of all tests to normal.

A small percentage of acute hepatitis goes into a chronic phase. This is diagnosed if clinical and laboratory evidence of hepatitis persists four months after onset. Predisposition to the chronic phase includes inadequate bed rest and treatment early, use of alcohol, intercurrent infections, older age at onset, previous liver disease and pregnancy. The prognosis is quite guarded.

Many cases clear completely while others go on to a relentlessly progressive cirrhosis that defies all the usual treatment. The treatment of chronic hepatitis is essentially that of cirrhosis and will not be considered here. If there is liver enlargement, a needle biopsy may aid in the follow-up of chronic hepatitis and early cirrhosis.

Prevention

The prevention of infectious hepatitis is that of avoidance of fecal contamination of food and water. Care should be taken with the excreta and blood of known cases. The prevention of homologous serum hepatitis is the avoidance of needle innoculation with infected blood or blood products.

The same syringe should not be used for multiple injections of different individuals even if the needles are changed, due to the possibile aspiration of small amounts of infected serum or blood. As there is no definite means of inactivation of whole blood or serum, these should be used with the knowledge that hepatitis may result at any time. Also there is no means of detecting infected blood, as even in well screened donor groups, from 0.1 - 0.5 per cent of cases result.

Carriers

It is thought that completely asymptomatic carriers with true negative histories may exist. Pooled plasma offers the greatest source of infection. If plasma is stored at room temperature for six months, nearly all the hepatitis virus is destroyed. None of its properties except that associated with blood clotting is affected by this storage. It is then safe to lyophilize and freeze it as usual. It is best to use dextran, albumen, or glucose and water instead of blood products except when real indication for the latter exists. The mortality of serum hepatitis is as high as 10 per cent in some series and the resulting morbidity from chronic hepatitis and cirrhosis is much higher.

Gamma Globulin

Gamma Globulin. Protection against infectious hepatitis but not serum hepatitis will result if .06 cc./lb./ body weight is given more than one week prior to the expected onset of symptoms, or within the first seven to ten days following exposure. This is chiefly useful in large families or institutions or in debilitated or pregnant individuals known to have been exposed.

Summary

1. Viral hepatitis, including infectious hepatitis and homologous serum hepatitis has become a more severe disease with more sequelae in recent years.

2. Many liver function tests have been devised to aid in the diagnosis and treatment.

3. Treatment consists chiefly of diet, rest, vitamins, and in selected cases - other specific measures.

4. Prevention includes adequate sanitary measures, care in the use of blood and blood products and the use of gamma globulin in suitable cases.

CLINICAL NOTES FROM GRAND ROUNDS

These notes are abstracts of opinions expressed by staff members during case presentation at the Friday Grand Rounds of the Pratt Diagnostic Clinic—New England Center Hospital.

Patients with cold hemagglutinins in very high titers occasionally develop acrocyanosis and peripheral vascular symptoms upon exposure to cold because of intravascular agglutination of red cells. More serious internal trouble does not occur because the process is rapidly reversible at body temperature.

Clinical Experience with a New Sedative*

By Walter Z. Baro, M. D., Azusa, California

Sleeplessness, anxiety, excitement and depression are symptoms frequently seen in general practice as well as in the practice of psychiatry; and, although tremendous progress has been made in the fields of drug therapy and psychotherapy, these disturbances appear to be more to the forefront. While every effort should be made to determine the etiology of these most often distressing symptoms some form of therapy is indicated in order to place these patients at ease and more receptive to treatment.

The list of drugs available for the treatment of insomnia and anxiety is too long to discuss here; but while some of these agents have proven useful, they leave much to be desired.

Interesting Combination

More recently, my attention was drawn to an interesting combination of drugs known as Plexonal.* Baer (1) reported his observations with this combination for the treatment of insomnia and anxiety in 133 cases. He found that the addition of Dihydroergotamine to the three barbiturates and scopolamine, potentiates the sedative effect resulting in a more specific action. Furthermore, smaller doses of barbiturates are needed to give the same effect and the combination of the barbiturates is better tolerated. He also found that the presence of Dihydroergotamine in this combination made it possible to reduce the amount of scopolamine considerably and yet the hypnotic effect was of longer duration and more profound. Rothlin (2) has shown that Dihydroergotamine exerts a central sedative effect, analagous to that of ergotamine, as well as a stronger peripheral adrenosympathicolytic effect.

Sedative Effect

Pritzker (3) and Schneider and Wiemers (4) found that Dihydroergotamine exerts a sedative effect in certain forms of psychomotor excitement but in higher doses than are usually required in autonomic and psychotic disturbances. Boss (5) employed this combination for about two years with excellent results and without side effects. Binswanger (6), Schneider (7) and Laberke (8) reported gratifying results with the preparation in a rather large number of patients as a hypnotic and sedative. Kowalsky (9) observed the effects in 149 patients. He refers specifically to the effectiveness after deliveries and operations, with favorable results in the convalescence. Scherer (10) used the combined drugs as a hypnotic and sedative in surgical patients and Nymgard (11) reported excellent results as a hypnotic and sedative in the treatment of senile overexcitation and sleeplessness. Walter (12) treated 100 hospitalized patients for sleeplessness due to organic nervous diseases and autonomic disturbances, with a high percentage of results. Kral and Krauser (13) employed the preparation in 73 psychiatric patients and reported best results in anxiety and tension states and sympathetic over-activity.

Variety of Disorders

This report deals with 53 patients complaining of a variety of psychiatric disorders. Plexonal was used principally as a daytime sedative and the average dose was one tablet three times a day. Of the 53 patients treated, 34 cases had excellent results, eight good, nine fair and two poor. The psychiatric disorders treated consisted of eleven anxiety state cases, six situational neurosis, ten menopausal neurosis, sixteen psychoneurosis, two traumatic neurosis, two senile neurosis, three psychopathic personality with anxiety state, one with Marie-Strumpell disease, disc surgery, demeral addiction, withdrawal state, psychoneurotic depression, one with chronic rheumatoid arthritis with mild anxiety state and one with dementia praecox, simple type.

Various Barbiturates

Prior to the present study, these patients were treated with various barbiturates, but in many cases they were discontinued because of side effects. In this series of 53 cases treated with Plexonal there was one patient who was known to be allergic and developed an allergic dermatitis. One other patient experienced dizziness, but reacted in a similar manner to other sedatives, even in minute doses. I have found the preparation an excellent sedative to prepare a patient with various psychiatric disorders, for psychotherapy. All patients experienced sedation and a general feeling of well-being.

CASE REPORTS

Case No. 1

W. T. is a 27 year old married male. He came under my care in August 1953. He has been suffering from a long standing severe anxiety state. The first impression was that he may even be a schizophrenic personality. Outside of psychotherapy, he was placed on Dexamyl with only very slight improvement. He was placed on Plexonal in March of 1954, 1 tablet three times a day which gradually was reduced to 1 tablet twice a day. Within one week to ten days a definite improvement was noted. His anxiety symptoms disappeared. It was noted that three tablets a day were too much, causing an occasional dizziness. Six weeks after initiating Plexonal, the patient indicated that "he felt better than he has ever felt since his anxiety state started." He describes his well-being by stating that "he has not a worry in the world" that "he does not get upset about any-

* Sodium diethylbarbiturate, 45 mg; Sodium phenylethylbarbiturate, 15 mg; Sodium isobutylallylbarbiturate (Sandoptal), 25 mg; Scopolamine hydrobromide, 0.03 mg; Dihydroergotamine methanesulfonate, 0.16 mg. Furnished by Sandoz Pharmaceuticals

thing" that "he has begun to mix with people, which he did not do before" that "he has found new interests and that he gets along better with other people." The result in this case is excellent.

Case No. 2

K. Z. is a 52 year old white married male. He came to my attention on December 22, 1953. He was diagnosed at that time as a questionable thrombosis of the spleen and essential hypertension with severe psychoneurosis. His blood pressure ran about 170/90 until he was placed on Plexonal. Six weeks after Plexonal medication his blood pressure on both arms was 120/80. The result of this patient's case should be considered excellent.

Case No. 3

W. L. is a 25 year old white married male. He was first seen in October 1953. Diagnosis: Constitutional psychopathic inferiority with superimposed anxiety state. He was given Plexonal in March. Since the patient has been under Plexonal all his anxiety symptoms are gone and the result is excellent.

Case No. 4

E. C. is a 57 year old woman. Diagnosis: Menopausal neurosis. She was first seen the beginning of April 1954 with a very severe emotional upset accompanied by vomiting, nervousness, aches and pains all over her body and hot flashes. The combination of Plexonal and estrogenic hormone was started. The patient reported on her third visit that she felt better than she has felt in years — as a matter of fact she felt that there was no reason or necessity for seeing me. The results should be considered excellent.

Case No. 5

L. S. is a 23 year old married female. Diagnosis: Grand mal and petit mal epilepsy with severe psychoneurotic overlay — possibly causing the epileptic seizures. This patient has had epilepsy since the age of 14 years. It became quite apparent that many of her grand mal and petit mal seizures were definitely related to nervous upsets. The patient had had no serious grand mal seizures recently until her husband amputated part of his right index finger. This produced one gran mal seizure after the other. The patient was placed on Mesantoin and Hydantal antiepileptic therapy which curbed her grand mal seizures but not her petit mal seizures. She then was given Plexonal, one tablet three times daily. The patient has been seizure free and free from any nervous upsets for 30 days.

Discussion

Plexonal has proved to be an ideal daytime sedative. The combination of three barbiturates with Dihydroergotamine and Scopolamine is rational and has been found to be superior to many other sedatives. Fifty-one of the fifty-three patients obtained the desired sedation and a feeling of well-being. The average duration of treatment was two months or more. In my experience it has proved to be an excellent combination for ambulatory patients and it was useful in the preparation of the patient for psychotherapy.

Summary

1. Plexonal produces a high percentage of excellent results as a daytime sedative.
2. It produces fewer side effects and is longer acting than other sedatives previously employed.
3. It is a useful agent as an adjunct to psychotherapy.

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CLINICAL NOTES FROM GRAND ROUNDS

These notes are abstracts of opinions expressed by staff members during case presentation at the Friday Grand Rounds of the Pratt Diagnostic Clinic—New England Center Hospital.

Massive ascites may be reduced gradually through the use of a polyethylene tube inserted into the abdominal cavity by means of a special needle or trocar, the needle being removed after the tube is in place. The tube, with several openings made in its intra-abdominal portion, is held in place by a single suture. The other end of the tube is inserted into a bottle, a pinchcock controlling the rate of flow. The flow is adjusted so that it takes from 36 to 48 hours to reduce the pressure of the fluid in the abdomen. During this time the patient is free to move about in his bed. Advantages of the method are that it may be used without causing much psychic or physical trauma in acutely ill patients, and pressure adjustments are made gradually rather than acutely. Because of the slight danger of introducing infection by this method, prophylactic antibiotic therapy should be used during the procedure.

Cardiac Arrest

By Jack T. Rush, M. D., F. A. C. S., El Paso

Sudden death in the operating room or clinic following anaesthesia is not new, but it was not until recent years that the physiological basis for cardiac arrest was understood.

By definition cardiac arrest is that condition in which there is an inadequate amount of oxygenated circulating blood to sustain life. This is a very broad definition and a more accurate definition one should include the statement "for no demonstrable reason", many deaths in the operating room occur due to pulmonary embolus, cerebrovascular accident, asphyxia, overdose of anaethesia, coronary thrombosis hemorrhage, etc.

The incidence of cardiac arrest varies with different clinics being higher where there is a large amount of cardiovascular surgery performed. At the Johns Hopkins Hospital 5.5 per cent of cardiac surgery cases develop arrest.[1] While Beecher and Todd[2] report death in each 2680 anaesthetics. Statistics taken from 30 large medical centers by Stephenson et al. reveal one case of cardiac arrest in 2384 operations. The sex incidence is 61 per cent male and 39 per cent female. 86 per cent occurred in the operating room; 14 per cent occurred outside the operating rooms.[3]

Two Types

There are two types of cardiac arrest each having a well explained physiological etiology. In ventricular fibrillation, which accounts for only 10 percent of cardiac arrests seen surgically, there is an excessive cardiac reaction to epinephrine. This excessive action of epinephrine which may be due to excessive production of epinephrine due to fear, excitement, or drug reactions.

The myocardium may be chronically damaged and more susceptible to the action of epinephrine. Cold will also produce ventricular fibrillation in experimental animals. In cardiac asystole, which accounts for 90 per cent of cardiac failures seen surgically, the etiological agent is excessive action of acetylcholene which is produced at the myoneural junctions in the heart secondary to vagal stimulation.

Anoxia plays a most important role in cardiac arrest because it inhibits cholinesterase which normally destroys excess acetylcholene and also sensitizes the myocardium to the effect of acetylcholene. Cardiac arrest occurs when the coronary blood pressure is maintained below 70 mm. Hg. for one-half hour. Stimulation of the vagal reflex by handling the hilum of the lung, bronchus, esophogus, pharynx, or structures in the neck may initiate cardiac arrest.

Warning Signs

Warning signs such as bradycardia, tachycardia, or extra systoles should alert the anaesthesist that something is wrong. Prophalaxis is most important. Elderly patients and those with known cardiac disease should have an electrocardiogram and cardiac clearance before elective surgery.

Maintenance doses of digitalis or quinidine should be continued but toxic doses must be avoided. The hilum of the lung should be infiltrated with 1 per cent procaine during chest surgery. Protect the vagae nerves and carotid bodies from stimulation.

The blood pressure should be maintained at near normal levels to prevent shock and anoxia. Whole blood, plasma, dextran, Vasoxil, Levophed, or neosynephrine may be used to maintain blood pressure.[4]

Atropine has been highly recommended as a prophylactic agent, but in my experience has not proven to be of any benefit in preventing vago-vagal syndrome.

Perhaps newer anticholenergenic drugs such as Banthine, Monodral, Antrenyl, etc., would be more efficacious, but results of such experiments have not been reported.

Diagnosis

The diagnosis of cardiac arrest is the joint responsibility of the anaesthesist and the surgeon. The anaesthesist should know the pulse rate, respiratory rate, and blood pressure at all times. The surgeon should note the color of the blood, the warmth and color of the tissues, and the presence or absence of arterial pulsations. Working as a team the surgeon and anaesthesist should make the diagnosis immediately by the following signs:

1. Imperceptible pulse and blood pressure.
2. Labored respiration which soon stops.
3. Absence of bleeding.
4. Cyanosis followed by pallor.
5. Widely dilated pupils.
6. Inaudible heart sounds.
7. Stoppage of direct writing EKG.

In no other condition is the cooperation between the surgeon and anaesthesist so important. After warning the surgeon of the cardiac arrest the anaesthesist should introduce an endotracheal tube and administer 100 per cent oxygen at the rate of 20 - 24 respirations per minute at a pressure of 12 mm. hg. There is no time for consultations or to call another surgeon.[5]

Delay is fatal. The doctors present must carry out cardiac resuscitation immediately. Do not attempt to stimulate the heart by injections of Adrenalin through the chest wall. The surgeon must open the left Chest through the 5th or 6th interspace.[6] In men this is the intercostal space just below the nipple.

No Antiseptic

No antiseptic is needed on the skin—there will be no bleeding. The internal mammary vessels may be

avoided by staying one inch lateral to the lateral border of the sternum.

If these vessels are cut they may be ligated later. The costal cartilages are cut to allow more room for the wrist. The pericardium is opened and the fingers of the right hand are placed behind the ventricles with the thumb in front. The heart is then intermittently compressed at the rate of about 80 per minute.

The table should be put in marked Trundelenburg position to increase cerebral circulation. Intravenous fluids should be administered rapidly so that the right side of the heart will fill between compressions.

The aorta should be compressed by an assistant.

If the heart fails to respond after a brief period of massage ½ cc 1/1000 epinephrine in 5 cc. saline should be injected into the left ventricle.

Weak Heart Beat

If the heart beat is weak 10 cc 10 per cent calcium chloride injected into the left ventricle will greatly increase the force of the contractions and may stimulate the heart that fails to respond to massage.[7] Calcium gluconate is not suitable as it is poorly ionized and does no good.

If the heart is in fibrillation it should be defibrillated by means of an electric defibrillator which shocks the heart into standstill and then it must be massaged to get it started again.

There are several commercial defibrillators on the market and one may be constructed cheaply in any shop.[8] One hundred ten volt current is run through a resistance coil of 19 ohms. The electrodes should be at least 1½ inches in diameter so as not to burn the surface of the heart. One electrode is placed behind the apex and the other at the A. V. junction.

Current Applied

Current is applied by means of a hand or foot switch for .1 to .5 seconds. The force of the shock will make the whole body hump and may have to be applied from one to five times in order to stop the fibrillation. After the heart is defibrillated it should be bathed in 1 per cent Procaine and 10 cc. 1 per cent Procaine injected into the left ventricle to reduce cardiac irritability.[9]

The heart is then massaged in the usual manner until normal rhythm has been established. It is necessary to have two or more doctors to massage the heart as it is very fatiguing and the massage may have to be carried on for 30 minutes.[10]

Dr. Zoll of Boston has developed an artificial pace maker which regulates the heart in patients with complete heart block and can start the heart in experimental animals, and has been successful in two human patients.[11]

Heart Observed

The heart should be observed for 20 minutes after it has resumed normal rhythm. The pericardium should be closed loosely as considerable pericarditis develops after massage. The chest is drained by an intercostal tube attached to an under water seal bottle and the chest closed in layers.

Post operative care is the same as for any thoracotomy operation. There is usually a tachycardia for several days and not infrequently some irregularity.

Prognosis depends on the condition of the patient for whom the original operation was performed as well as the duration of time that the heart was stopped. Three minutes is the upper limit that the heart can be stopped without resulting in brain damage. After the heart has been stopped for eight minutes it is usless to massage the heart.[12]

Report On Cases

Barber and Madden[13] in reviewing the literature from 1924 to 1946 found 44 cases reported with complete recoveries in 23 cases, or 52 per cent. Bost[14] in a review of literature from 1946 to 1950 found 34 reported cases with 21 complete recoveries or 60 per cent. From 1924 to 1950 there were a total of 178 reported cases with 69 complete recoveries or 38 per cent. Stephenson et al[3] reported a review of 1200 cases reported up to the present time with 28 per cent complete recovery.

In my own experience I have seen approximately 50 cases with six complete recoveries. In many cases the heart will respond with normal rhythm and the patient appears to be doing well, but the pupils remain dilated and the patient remains in a decebrate state.

There is one patient still living in such a condition for over two years. Most patients who have brain damage will die of pneumonia in a few weeks.

Electroencephalographic studies of these patients reveal a normal sleep wave with blockage of afferent impulses in the brain stem. At autopsy the brain appears normal but minute areas of focal necrosis are found in the brain stem.

Conclusion

In conclusion I would like to state that every physician and surgeon should be trained to perform cardiac massage as it may occur any place or anytime that an anaesthetic is used. An emergency pack should be kept sterile in all clinics and operating rooms containing the following supplies:

2 scalpels
2 hemostats
2 pair scissors
2 5cc syringes
2 No. 20 spinal needles
2 No. 18 spinal needles
2 ampules of 1/1000 epinephrine
2 5cc ampules of 10 per cent procaine solution
2 10cc ampules of 10 per cent calcium chloride

The following procedural guide should be posted

in all operating rooms and clinics. Every doctor should be familiar with the steps of cardiac resuscitation.

Procedure to Follow In Cases of Cardiac Arrest

1. Make diagnosis immediately by absence of pulse.
2. Establish an airway and give artificial respiration with respirator, anesthetic machine, or mouth to mouth breathing.
3. Open the left chest through the fifth interspace. Make incision just below the nipple from the sternal border to posterior axillary line. Open the pericardium, insert hand with fingers behind the heart and thumb in front. Intermittently compress the heart at a rate of 60-100 beats per minute.
4. Call For Surgical Assistance. Get anesthetist with gas machine to give 100 per cent oxygen through endotracheal tube.
5. Insert a large needle in a vein (15 gauge) and administer fluids rapidly to fill the patient's heart.
6. Lower the head of the table to increase cerebral circulation.
7. If heart does not begin to beat after 3 minutes, inject ½ cc. 1/1000 Adrenalin in 5 cc. procaine into left ventricle. 2 - 4 cc. 10 per cent Calcium Chloride will increase heart tone.
8. If fibrillation develops, call for defibrillator in Main O. R.
9. Observe the heart for 20 minutes after heart has resumed beat, to make sure it does not stop.
10. These instructions are to be carried out *by the physician present* at the time of cardiac arrest.

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CLINICAL NOTES FROM GRAND ROUNDS

These notes are abstracts of opinions expressed by staff members during case presentations at the Friday Grand Rounds of the Pratt Diagnostic Clinic—New England Center Hospital.

In bronchial asthma associated with secondary (anoxemic) polycythemia, cor pulmonale, and right ventricular failure, energetic therapeutic measures are necessary. Venesection, with reduction of hematocrit values to normal or slightly above, is often helpful—and of course, full digitalization, mercurial diuretics, and a low sodium diet are indicated. ACTH or cortisone therapy should *not* be withheld if either is necessary to control the asthma, because when bronchospasm and its attendant increased respiratory efforts are reduced, the work of the heart is lessened. A new type of positive pressure breathing apparatus called a "pulmonary ventilator" has been used to improve gas exchange in the lungs, relieving anoxia and reducing carbon dioxide retention. With this device, nebulized epinephrine, isuprel, and antibiotics may also be introduced into the lungs under pressure. It has also been noted that Diamox, a carbonic anhydrase inhibitor, is particularly helpful in this disorder because it promotes bicarbonate excretion in the urine, bringing about a reduction in the serum bicarbonate and an increase in the serum chlorides, thus potentiating the effectiveness of mercurial diuretics. (It is well known that ammonium chloride may be harmful when there is respiratory acidosis.)

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When acute surgical emergencies develop during convalescence from acute myocardial infarction, necessary surgery should not be unduly delayed; with modern anesthesia methods even these patients tolerate surgery surprisingly well, and delay may serve to still further weaken the already damaged heart. In such cases, of course, the minimum amount of surgery should be undertaken, any necessary secondary operation being performed later at a time of election.

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The most likely causes of a sudden change in personality in a person over the age of sixty are: subdural hematoma, malignant brain tumors, or metastatic malignancy. The differential diagnosis is of utmost importance because in subdural hematoma the prognosis is good if the condition is recognized early in its course and promptly treated surgically.

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Hypertrophy of the gums is one of the early signs of acute monocytic leukemia. A new nitrogen mustard compound known as "GT41" has been shown to have a depressive effect on monoblasts, and may have a temporarily beneficial effect in monocytic leukemia.

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Vitamin K and Its Indications

By Carlos Albores, M. D., Torreon, Coahuila, Mexico

This Vitamin is very widely used. It is prescribed by pharmacists and midwives for any hemorrhagic suffering, but we doctors also use it without indication or usefulness in hemorrhages brought about by abortions, metrorrhagia of endocrine origin, for tumors of the uterus, and in childbirth. There are surgeons who use this Vitamin as preoperative routine and the N T E use a wonder blend, Vitamin K and Coagulen before tonsillectomies. It is used for haematemesis caused by ulcers, for haemoptysis caused by tuberculosis or cancer, haematurias and even for wounds which bleed profusely.

Vitamin K

Vitamin K is an essential dietetic substance for blood coagulation. In 1929 Dam observed how chickens fed with little grease would acquire a disease characterized as spontaneous hemorrhages which he believed were caused by the diminishing prothrombin contained in the blood. This disease was promptly cured with alfalfa and other green plants. Dam himself named the substance found in these foods thusly: Vitamin K (Koagulation).

A little later, Quick found the same thing in people sick with jaundice. Hawkins and Whipple found the same thing in blood of dogs with biliary fistula.

In 1938 Butt and Warner pointed out the effectiveness of Vitamin K and biliary salts found in hemorrhagic diathesis of jaundice patients. Almquist and Stokstd show that Vitamin K is a lipid soluble substance and is found in alfalfa, in vegetable oils, in decayed proteins, in fish, in casein, etc.

In 1939 Doisy separated Vitamin K from alfalfa, chemically 2-metil-3-fitil-4-naftaquinona, hence the knowledge of the chemical activity of the quinone.

Principally, the menadione is used, a crystalline powder, brilliant, odorless, insoluble in water, soluble in alcohol and in vegetable oils. There are also derivatives such as sodium bisulphite of menadione which is soluble in water and which is used frequently.

Action of Vitamin K

Vitamin K is indispensable to maintain the prothrombin found in sanguineous plasma at a useful level; that is, it is a very important element in the mechanism of sanguineous coagulation.

We all know the important part that prothrombin plays in the intricate mechanism of sanguineous coagulation; and precisely, it is Vitamin K which is intimately related with the complex synthesis of this protein, prothrombin, which surely takes place in the liver, and although its intimate mechanism is unknown it is supposed that Vitamin K works as a prosthelic group for an enzyme in the synthesis that hepatic cells make of prothrombin. Surely Vitamin K combines itself with an apoenzyme forming an active enzyme which makes prothrombin.

Milligram Daily

If there should not be sufficient Vitamin K, and we only need one milligram daily, the prothrombin level lessens, and as a result there is a deficiency in coagulation and a tendency to hemorrhage. It is insufficiency of Vitamin K that repels in the synthesis of prothrombin and in turn in sanguineous coagulation.

Therefore, when there is a deficiency and only then is Vitamin K indicated. In no other circumstance is it anti-hemorrhagic, nor coagulant, nor hemostatic; and fortunately its deficiency is not frequent, as the organism obtains it easily from food.

Are all hypoprothrombinemias caused by a deficiency of Vitamin K?

What disorders contribute to hypoprothrombinemia?

Disorders Listed

a. Toxic or infectious hepatitis with hepatic insufficiency. Vitamin K is useless in this case because of the lessening of prothrombin caused by damaged hepatic cells therefore, prothrombin is not synthesized.

b. The lessening of prothrombin caused by a deficiency in the absorption of Vitamin K in the intestine because of biliary obstruction—bile is indispensable for its absorption—or by ingestion of sulfas that modify the bacterial population, which is also necessary. Vitamin K is suggested in this case.

c. By deficient nourishment, especially in the newborn because his intestinal flora has not yet developed.

d. By anti-coagulant or antagonistic drugs which probably hinder the synthesis of prothrombin, neutralizing the action of Vitamin K.

The above enumeration points out that not all hypoprothrombinemias improve with Vitamin K and that one of the tests for examining the hepatic function (Koller), is based on the administration of Vitamin K, which normalizes sanguineous prothrombin 24 hours after its injection and is negative in case of damaged hepatic cells.

Review

Let us review the reasons for hemorrhage, and may we stress that there are few caused by an insufficiency of prothrombin and that nearly all the sanguineous losses are due to other reasons, the motive for which Vitamin K is useless.

Causes for Hemorrhage

A. Injury of the large blood vessels brought about by traumatism. The wearing away of vessels through pathologic processes.

B. Deficiency in vascular function.
  1. Multiple Hereditary Telangiectasis.
  2. Purpura not thrombocitopenias.
  3. Lack of Vitamin C (Scurvy) and P.

C. Brittleness of skin and vessels. (Ehler's Syndrome — Danels).

D. Failure of Factors Intervening in Coagulation.
  1. Quantitative Deficiency of platelets.
  2. Qualitative Deficiency of platelets. (Hemophilia).
  3. Diminished Prothrombin.
    a. Absence of Vitamin K.
    Jaundice caused by obstruction, biliary fistula, deficient intestinal absorption, scarce diet, disappearance of or diminished intestinal bacterial population, by sulfas or antibiotics, hemorrhagic disease of the newborn.
    b. Hepatic Injuries.
    c. Toxics, dicumarol, salicylates.
  4. Diminished fibrinogen.
    a. Constitutional Congenital Fibrinogenia.
    b. Serious hepatic injury.
  5. Excessive quantities of anti-coagulants in the blood.
    a. Heparin.
    b. Hyrudin.
    c. Dicumarol, Troxoman, etc.

Sometimes Useful

After having mentioned the causes for hemorrhage and bearing in mind the physiological function of Vitamin K, we have to come to the conclusion that it is useful only when prothrombin has decreased because of an insufficiency of said vitamin, provided the hepatic cell functions correctly.

When we use Vitamin K for other hemorrhagic conditions, it is uselessly and improperly prescribed, and when used for conditions not hemorrhagic, as is advised by the same laboratories producing said vitamin, it is done empirically; as there is not sufficient physiological basis to render it useful for coeliac disease, for chilblain, for arterial hypertension, and for whooping cough.

Therapeutic Uses of Vitamin K

1. It should be used for biliary obstruction or for fistula, and prophylactically for patients with jaundice who are to undergo surgery, even when prothrombin blood activity is normal. From five to ten milligrams as a daily requirement is sufficient.

2. When there is defective absorption of Vitamin K and there exists a hypoprothrombinemia as it is prone to be with sprue, regional enteritis, dysentery, and after wide resections of the intestine, Vitamin K is indicated.

3. There exists in the newborn a physiological hypoprothrombinemia which at times originates hemorrhagic diseases in the child. Although not everyone sustains a deficiency of Vitamin K as etiology, taking into account it is an innocuos procedure and if it can prevent a good many deaths among the newborn, it can readily be used as routine with them. Antagonism between anti-coagulant drugs and Vitamin K is a solid basis so that it may be used to counteract or retain the action of anti-coagulants which are actually being used frequently.

4. The hypoprothrombinemia caused by salicylate ingestion or sulfas and streptomycin responds very well to Vitamin K.

5. Vitamin K should be given to counteract the actions of anti-coagulants when necessary.

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Diabetic retinopathy is characterized by the appearance of punctate microaneurysms of capillary vessels that develop in clumps, often with surrounding exudates and hemorrhages. The small aneurysms look like petechiae but may persist for weeks or months; they eventually become hyalinized, however, and remain as white dots. There is high correlation between the appearance of diabetic retinopathy and the development of Kimmelstiel-Wilson lesions in the kidney. These manifestations of diffuse vascular disease, as well as arteriosclerosis and hypertension, may occur despite good diabetic management, but are most common in poorly controlled diabetics.

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Panhypopituitarism and anorexia nervosa bear only a superficial resemblance to each other. Anorexia nervosa is poorly named, in that there may not be anorexia; indeed, the appetite may be excessive but well-controlled even in the weight-losing phase. Sprees of excessive eating may be observed. It is a disorder of women, by definition, and occurs in early adult life. Amenorrhea and severe loss of weight are essential features. A bland attitude and a deceptive manner of not eating while food disappears are common. The disease is to be regarded as a serious mental disorder.

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Panhypopituitarism affects both sexes, is only occasionally associated with severe loss of weight. and may follow an abnormal and hemorrhagic delivery, be caused by pituitary tumor or ablation, etc. Amenorrhea, atrophy of the testes, thyroid insufficiency, loss of hair growth, and hypoglycemic episodes may be observed. Cortisone is helpful in this disease but not in anorexia nervosa.

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Strontium chloride has been advocated for the treatment of senile and postmenopausal osteoporosis and is alleged to give relief from pain for so long as its administration is continued.

Clinical Note on Cautery of Cervical Lesions

By Joseph B. Raddin, M. D., Phoenix

Etiology

Cervical erosions, Nabothian cysts, edema of the cervix, and pelvic parametritis are commonly the result of endocervicitis. The usual cervical erosion is due to irritation by the discharge from the cervical canal gland infection flowing over the cervix.

Therapy

1. Cleanse the cervix and cervical canal of discharge. Do not be too vigorous.

2. Negetan (Lilly) is applied by cotton swab to the cervical canal and to the erosion, taking precautions to protect the vaginal mucous membrane with a piece of gauze from contact with the Negetan.

3. Insert a medicated vaginal tampon which is retained for 24 hours.

This treatment is repeated three times weekly during the interval between menstruation.

Acetic acid douches, three or four tablespoonfuls of white or distilled vinegar to one quart of warm water, is used daily between tampon treatments. A douche each morning during menstruation until the cervix is healed is routinely prescribed to prevent a flareup of the cervical canal gland infection.

Cautery Is Not Indicated For Most Cervical Lesions

Cautery of most cervical erosions is not necessary when the conservative therapy suggested is used.

Cautery of the cervical canal glands for infection is not necessary nor desirable because of the frequency of cervical canal stenosis subsequent to effective cautery.

Radical conization by knife or cautery is not desirable because excessive scar tissue and stenosis is a common sequel.

Cautery Is Indicated For Few Cervical Lesions

Cautery destruction of Nabothian cysts is always indicated. It should be thorough but not excessive.

Cautery of the base of cervical polyps is desirable.

A large ugly looking cervical erosion may be cauterized after biopsy has been reported negative for carcinoma.

Summary

Cautery of cervical lesions is commonly indicated only for Nabothian cysts, cervical polyps and large cervical erosions. Frequency of cervical canal stenosis contraindicates cautery and conization for endocervicitis.

Cervical erosions regularly heal promptly without cautery when the cervical canal gland infection is treated in the manner suggested. Large chronic cervical erosions often heal rapidly without cauterization.

Carcinoma of the cervix is considered to be a common sequel of chronic cervical erosion. Treatment of endocervicitis thus cures and prevents cervical erosions and is also prophylactic therapy for carcinoma of the cervix.

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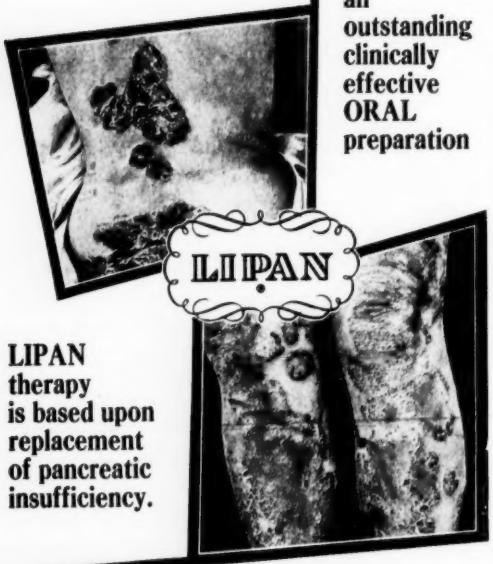
Spontaneous deficiency of pantothenic acid in humans is unlikely because of its wide distribution in nature. Increased demands or impaired utilization are theoretically possible. Recently pantothenic acid deficiency was induced in human volunteers by the combined use of a purified and chiefly synthetic diet deficient in this substance and a metabolic antagonist, omega-methyl pantothenic acid. In the second week of the period on the deficient diet a fall in the diastolic pressure and lability of the systolic pressure became evident, and later there were fatigue, anorexia, constipation, irritability, paresthesias, and susceptibility to upper respiratory infections. There was laboratory evidence of adrenal cortical hypofunction. The symptoms and signs subsided following restoration of a normal diet. Whether or not these findings are of clinical significance remains to be proved.

✤

In pulmonary sarcoidosis ventilatory studies are usually normal except for a slight restrictive defect; there is, however, a diffusion defect due to disease in the region of the alveolo-capillary membrane. Other diseases may be pathologically indistinguishable from pulmonary sarcoidosis, notably: pneumonitis resulting from inhalation of beryllium dust, eosinophilic granuloma, and certain cases of tuberculosis. In sarcoidosis there is reduction of skin sensitivity and the tuberculin test is almost always negative; there may be hyperglobulinemia; in about one-quarter of the cases there is hypercalcemia often complicated by renal calculi. Because of the possibility of tuberculosis in these cases, material removed at biopsy should be inoculated into guinea pigs. The Nickerson-Kveim test (performed by intracutaneous injection of sterilized material obtained from lymph nodes or spleens of patients with sarcoidosis and later biopsy of the injected area) probably is non-specific and therefore is not always diagnostic even when positive. Treatment is often not necessary. Adrenal steroids may be useful, but because there is danger of tuberculosis, they should be covered with isoniazid and/or streptomycin and para-aminosalicylic acid (PAS).

NOW for PSORIASIS...



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Clinical evidence indicates psoriasis may be due to a disturbance of the lipid metabolism, evidently caused by a deficiency of pancreatic enzymes.*

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LIPAN — and nothing but LIPAN, as maintenance regimen may keep patients free of lesions.*

**References available.*

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